REMARKS

Claims 1, 3-5, 7-14, 17, 31-55 and 57-96 were pending in this application. By virtue of this response, claims 1, 9, and 17 are amended, claims 91-93 are cancelled. Upon entry of this amendment, claims 1, 3-5, 7-14, 17, 31-55, 57-90, and 94-96 are under consideration.

Support for the amendment of claims 1, 9, and 17 can be found, for example, at page 7, line 26 of the specification, as well as previously pending claims 91-93. No new matter is added.

With respect to claim amendments and cancellation, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional applications.

Withdrawn Rejections

Applicants acknowledge with appreciation that the previous rejection of claims 1, 3-15, 17, 31-55, 57-90 under 35 U.S.C. § 112, second paragraph as being indefinite is withdrawn in light of the amendments of May 9, 2008.

Claim Rejections – 35 USC § 112

Claims 1, 3-5, 7-15, 17, 31-55 and 57-96 are rejected under 35 U.S.C § 112, first paragraph, as allegedly failing to comply the written description requirement. Specifically, the Examiner alleges that the phrase "less than about 30 minutes" does not have support in the specification as originally filed. Applicants respectfully disagree.

Solely in an effort to expedite prosecution and without acquiescing to the Examiner's rejection, claims 1, 9, and 17 have been amended to recite "30 minutes or less," which the Examiner

has acknowledged support. Page 2 of the Office Action. Applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph is obviated by the claim amendment.

Claims 1, 3-5, 7-15, 17, 31-55 and 57-96 are rejected under 35 U.S.C 112, second paragraph, as allegedly being indefinite for failing to particularly point out the distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that the phrase "less than about 30 minutes" is vague and indefinite. Applicants respectfully disagree.

As discussed above, claims 1, 9, and 17 have been amended to recite "30 minutes or less" solely in an effort to expedite prosecution. The rejection under 35 U.S.C. § 112, second paragraph is thus obviated by the claim amendment.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph and 35 U.S.C. § 112, second paragraph be withdrawn.

Claim Rejections – 35 USC § 103

Rejection based on Desai, Kunz, and Westesen

Claims 1, 3-5, 7-14, 17, 31-33, 38-41, 46-49, 54-55, 57-96 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Desai et al (U.S. Pat. No. 5,439,686, "Desai") in view of Kunz et al. (U.S. Pat. No. 5,733,925, "Kunz") in further view of Westesen et al. (U.S. Pat. No. 6,197,349, "Westesen"). Applicants respectfully traverse this rejection.

The present application is generally directed to methods of treating hyperplasia of non-cancerous cells in a blood vessel. The claimed methods comprise systemically administering an effective amount of a composition comprising an amorphous drug in nanoparticle form, coated with a coating consisting essentially of protein in 30 minutes or less (as amended). Applicants

respectfully submit that none of the cited references, alone or in combination, renders the amended claims of the present application obvious.

Specifically, Desai discloses delivering pharmacologically active agents in protein shell-containing microparticle compositions that obviate the need for toxic organic solvents. Column 3, lines 29-34 and 45-58 of Desai. This allows substantially water insoluble pharmacologically active agent be administered in smaller volumes and at reduced administration time relative to those required in the prior art. Column 3, line 65 to column 4, line 2 of Desai. However, Desai does not teach the claimed methodology of treating hyperplasia of non-cancerous cells in a blood vessel. Nor does Desai suggest that systemically administering a composition disclosed therein in 30 minutes or less would be effective in treating hyperplasia of non-cancerous cells in a blood vessel.

The Examiner acknowledges that Desai fails to teach "the method of the composition for treating non-cancerous hyperplasia," and relies on Kunz "to cure this deficiency only." Page 8 of the Office Action. Applicants respectfully submit that Kunz does not render it obvious to use the composition disclosed in Desai for treating hyperplasia of non-cancerous cells in a blood vessel.

As stated in Kunz, many considerations need be taken into account when developing a method for treating hyperplasia of non-cancerous cells in a blood vessel, such as restenosis. For example, an effective treatment would entail: a) delivering a large number of molecules into the intercellular spaces between smooth muscle cells, b) directing an inhibitory drug into the proper intracellular compartment, and c) optimizing the association of the inhibitory drug with its intracellular target while minimizing intercellular redistribution of the drug, e.g., to neighboring cells. Column 2, lines 37-46 of Kunz. Furthermore, because smooth muscle cell proliferation takes place over several weeks, according to Kunz, it would appear a priori that the inhibitory drug be administered over several weeks, perhaps continuously, to produce beneficial effect. Column 2, lines 47-50 of Kunz.

Kunz discloses methods that were developed to address the problems discussed above. First, Kunz discloses a targeted approach where the therapeutic agent is conjugated to a vascular smooth muscle cell binding protein or peptide. This allows the therapeutic agent be specifically targeted to vascular smooth muscle cells. Second, Kunz discloses "sustained release dosage forms", i.e., "a dosage form designed to release a therapeutic agent therefrom for a time period ranging from about 3 to about 21 days," or longer. Column 10, lines 7-11 of Kunz; see also column 3, line 63 to column 4, line 34 of Kunz. Microparticulates and nanoparticulates are discussed in the context of exemplary sustained release dosage forms. Column 14, line 34 to column 17, line 11; column 4, lines 22-34 of Kunz. These sustained release dosage forms allow sustained release of therapeutic agents to target cells, such as vascular smooth muscle cells that are accessible to local administration. Column 3, line 63 to column 4, line 3. The sustained release dosage forms can also be coupled to vascular smooth muscle cell binding proteins or peptides. Column 24, line 54 to column 26, line 28.[1]

Kunz is completely silent about systemically administering a composition comprising an amorphous drug in nanoparticle form, coated with a coating consisting essentially of protein in 30 minutes or less. Given the unique considerations identified in Kunz for effective treatment of hyperplasia of non-cancerous cells in a blood vessel (such as restenosis) as well as the solutions presented therein, one of ordinary skill in the art would not expect that systemically administering a composition comprising a drug in nanoparticle form, coated with a coating consisting essentially of protein, in 30 minutes or less would be effective in treating hyperplasia of non-cancerous cells in a blood vessel.

Furthermore, Applicants respectfully submit that Kunz would have led a person of ordinary skill in the art away from the claimed invention. Applicants respectfully draw the Examiner's attention to Example 7 of Kunz, which evaluated the therapeutic efficacy of a therapeutic conjugate containing Roridin A and a vascular smooth muscle binding protein (VSMBP). Two therapeutic

[1] Kunz also teaches administration of therapeutic agents that cause a dilation and fixation of a vascular lumen by

conjugates (VSMBP-RA2' and VSMBP-RA13') and one non-conjugated control therapeutic agent (free Roridin A or "RA") were administered intraarterially in about 3 minutes into a pig model. Histological examination revealed that the therapeutic conjugates resulted in marked inhibition of intimal smooth muscle cell proliferation (a hypertrophy score of 1-3). Columns 4-9 of Table 2. The non-conjugated control therapeutic agent, on the other hand, was ineffective (a maximum hypertrophy scope of 4). Column 3 of Table 2.

Given the fact that the therapeutic agent not conjugated to a targeting moiety was ineffective in inhibiting cell proliferation under the testing conditions of Example 7, a person of ordinary skill in the art would not have been led to believe that systemic administration of a composition that is not conjugated to a targeting moiety (such as compositions recited in the present claims) in 30 minutes or less would result in inhibition of cell proliferation and treatment of hyperplasia in a blood vessel.

Contrary to the teaching in Kunz, the present invention is directed to systemic administration of a therapeutic agent, for example, paclitaxel, in a nanoparticle form coated with a coating consisting essentially of protein in 30 minutes or less, which produces beneficial effect. Attached for review is *Exhibit* 1, a meeting abstract entitled "Systemic Nanoparticle Albumin-Bound Paclitaxel (nab-Paclitaxel) for the Prevention of In-Stent Restenosis (SNAPIST-II): A Randomized Comparison of Single Dose and Single Dose Plus Repeat Dose at 2 Months." As shown in *Exhibit* 1, a single dose of a composition comprising nanoparticles of paclitaxel coated with albumin (Nab-paclitaxel) administered intravenously was effective in inhibiting restenosis.

The Examiner points to Example 8 of Desai as allegedly teaching "the antineoplastic drugs such as taxol in protein shells and it is administered in less than 30 minutes." Pages 7-8 of the Office Action; see also Page 5 of the Office Action. Applicants respectfully note that Example 8 discloses "In vivo Bioavailability of Soybean oil Released from Polymeric Shells," not

---

inhibiting smooth muscle cell contraction, thereby constituting a "biological stent."

administration of a drug, let alone administration of a drug for treatment of hyperplasia of non-cancerous cells in a blood vessel. Furthermore, as discussed above, the mere teaching that a drug (such as paclitaxel) can be systemically administered at a relatively reduced administration time does not suggest that such administration regimen would allow effective treatment of hyperplasia of non-cancerous cells in a blood vessel. On the contrary, as discussed above, Kunz would have led a person of ordinary skill in the art to believe that short-term administration (such as systemic administration in 30 minutes or less) of a composition (such as compositions recited in the present claims), would be ineffective.

Although the Examiner clarifies on page 8 of the Office Action that "Kunz is not relied upon to teach the nanoparticles or the administration time," she points to column 25, line 20 to column 26, line 40 of Kunz as allegedly teaching protein-coated particulates. Page 5 of the Office Action. Applicants respectfully submit that this issue was addressed during the interview conducted on September 26, 2006 between the Examiner and inventor Neil Desai along with Applicants' representatives. During the interview, the Examiner suggested that claims be amended to recite "coated with a coating consisting essentially of protein" to distinguish nanoparticles recited in the claims from the particulates disclosed in Kunz. The claims were subsequently amended in accordance with the Examiner's suggestion, and the 35 U.S.C. § 103 rejection based on Kunz and Westesen was withdrawn in view of the claim amendment. *See* Office Action dated March 8, 2007. Applicants reiterate that the particulates disclosed in Kunz are sustained release dosage forms designed to release a therapeutic agent for 3 to 21 days or longer.

Westesen does not cure the deficiencies of Desai and Kunz discussed above. Specifically, Westesen is cited as allegedly teaching use of an amorphous form of a poorly water soluble drug to provide better solubility and bioavailability of the poorly water soluble drug than utilizing a crystalline form. One of ordinary skill in the art reading Westesen would not expect that systemically administering a composition comprising an amorphous drug in nanoparticle form, coated with a coating consisting essentially of protein, in 30 minutes or less would be effective in treating hyperplasia of non-cancerous cells in a blood vessel.

Accordingly, Applicants respectfully submit that Desai, Kunz, and Westesen, alone or in combination, do not render the claims obvious. Applicants respectfully request that the rejection be withdrawn.

Rejections based on Desai, Hunter, and Westesen

Claims 1, 3-5, 7-14, 17, 31-36, 38-43, 46-51, 54-55, 57-96 are rejected under 35 U.S. C. §103(a) as allegedly being unpatentable over Desai in view of Hunter et al. (U.S. Pat. No. 5,716,981, "Hunter") in further view of Westesen. Applicants respectfully traverse this rejection.

Desai and Westesen are discussed above. As discussed above, Desai does not teach the claimed methodology of treating hyperplasia of non-cancerous cells in a blood vessel. Nor does Desai suggest that systemically administering a therapeutic agent in nanoparticle form, coated in a coating consisting essentially of protein, in 30 minutes or less, would be effective in treating hyperplasia of non-cancerous cells in a blood vessel.

Hunter does not cure the deficiency of Desai. Specifically, Hunter does not teach or suggest that systemically administering a therapeutic agent in nanoparticle form, coated in a coating consisting essentially of protein, in 30 minutes or less, would be effective in treating hyperplasia of non-cancerous cells in a blood vessel.

The Examiner points to Example 7 of Hunter which discloses insertion of stent into a rat. Even though the Examiner has acknowledged at page 2 of the Office Action that in the claimed method "the composition itself is administered" in 30 minutes or less, she states that insertion of the stent would meet the claimed delivery time "since the composition is delivered to the site in less than 30 minutes (the time it takes to insert a stent is less than 30 minutes)." Page 12 of the Office Action. Applicants respectfully disagree.

The claims in the present application do not encompass administration by drug coated stent, and those skilled in the art would understand that delivery by stent is distinct from systemic administration. As Hunter states with regard to drug coated stent,

> [T]he anti-angiogenic composition should provide a uniform, predictable, prolonged release of the anti-angiogenic factor into the tissue surrounding the stent once it has been deployed.

Column 22, line 65 to column 23, line 1 of Hunter.

Hunter thus is taking a different approach by providing continuous exposure of a therapeutic agent at the disease site, as opposed to the short-term, systemic administration method claimed in the instant application.

The difference between systemic administration and administration by drug coated stent is also emphasized in the present application, which states,

> In accordance with yet another aspect of the present invention, it is surprisingly been found that invention compositions can markedly reduce the level of intimal hyperplasia or neointima formulation following systemic administration of said composition. This is contrary to the conventional wisdom that calls for coating of devices such as stents with the drug of interest and insertion or implantation of the device within the stenosed blood vessel in order to provide local delivery of the drug.

Page 8, lines 10 of the specification.

Thus, Applicants respectfully submit that the Examiner's reliance on Hunter's disclosure of administration by stent as teaching the administration method recited in the present claims is unfounded.

The Examiner alternatively points to column 37, line 67 to column 38, lines 1-10 of Hunter as alleged teaching administration intrarticularly and intravenously. Applicants respectfully submit that the paragraph the Examiner points to merely provides a generally statement that the

composition disclosed therein may be prepared for administration by a variety of different routes. It neither teaches systemic administration of a composition in 30 minutes or less for treatment of hyperplasia of non-cancerous cells in a blood vessel, nor suggests that systemic administration of a composition in 30 minutes or less would be effective in treating hyperplasia of non-cancerous cells in a blood vessel.

Thus, Desai, Hunter, and Westesen, alone or in combination, do not render claims of the present application obvious. Applicants respectfully request that the 35 U.S.C. § 103 rejection be withdrawn.

Rejections based on Desai, Kunz or Hunter, Westesen, and Gregory

Claims 36-37, 44-45, 52-53 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Desai in view of Kunz or Hunter respectively in view of Westesen, in further view of Gregory (Transplantation, vol. 59, pp. 655-661, 1995, "Gregory"). Applicants respectfully traverse this rejection.

Dasai, Kunz, Hunter, and Westesen are discussed above. As discussed above, these references, alone or in combination, do not render the claims of the present invention obvious.

Gregory is cited as allegedly teaching that rapamycin is an immunosuppressant which has an antiproliferative action that is useful in the treatment of arterial thickening after injury such as angioplasty. Gregory does not cure the deficiencies discussed above.

Accordingly, Applicants respectfully submit that the cited references do not render claims of the present application obvious and respectfully request that the 35 U.S.C. § 103 be withdrawn.

Rejection based on Hunter, Yapel, Kunz, and Westesen

Claims 1, 3-15, 17, 31-33, 34-35, 38-41, 42-43, 46-49, 50-51, 54-55, and 57-90 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hunter by itself or in view of Yapel (U.S. Pat. No. 4,147,767, "Yapel") in further in view of Kunz and Westesen. Applicants respectfully traverse this rejection.

The Examiner alleges that Hunter implicitly teaches the claimed administration by teaching insertion of a drug coated stent. As discussed above, claims of the present application do not encompass administration by drug coated stent.

In response to Applicants' arguments in the May 9, 2008 Response to Office Action, the Examiner alleges that delivery of drug via a stent "still provides systemic delivery of the drug since the drug is released into the body and blood stream, i.e., systemic administration." Page 18 of the Office Action. Such statement is unfounded and contrary to the knowledge in the art. Applicants respectfully submit that a person of ordinary skill in the art would not have considered deployment of a stent coated with a drug composition as a way of systemically administering an effective amount of the composition.

The Examiner further notes that the dependent claims "are directed to the administration intra-arterial and a device that delivers the composition, both of which include stents," and relies on page 11, lines 25-28 of the specification of the present application for support of her position that the present claims encompass administration by drug coated stent is misplaced. Applicants respectfully submit that Page 11, lines 25-28 of the specification, which refers to stent, merely describes an embodiment that is not claimed in the current claim set. Applicants direct the Examiner's attention to the response to Office Action filed on September 7, 2007, where Applicants cancelled claims directed to deployment of stent (claims 16 and 56).

Thus, Applicants respectfully submit that the Examiner's reliance on Hunter's disclosure of administration by drug coated stent as teaching the administration method recited in the present claims is unfounded.

The Examiner alternatively relies on Kunz as allegedly teaching the claimed administration time. However, as discussed above, Kunz does not teach or suggest methods comprising administering to a subject an effective amount of a composition comprising an amorphous drug in nanoparticle form, coated with a coating consisting essentially of protein, wherein the effective amount of the composition is systemically administered in 30 minutes or less.

The Examiner refers to Examples 3, 5, and 14 of Kunz as allegedly teaching the claimed administration time. Applicants respectfully submit that the Examiner's reliance on Examples 3, 5, and 14 are out of context. Example 3 states,

> For administration by i.v. catheter, it is desirable that the therapeutic conjugate of the invention be administered in less than 3 to 5 minutes, so that blood flow can be reestablished in the patient. Therefore, studies were conducted to determine the binding kinetics of a smooth muscle binding protein with a Ka of $>10^9$ liter/mole.
>
> Column 46, lines 18-22 of Kunz.

After making a general statement regarding desirability of delivery time for a certain mode of delivery of the therapeutic conjugate, Example 3 goes on to discuss the *in vitro* experiment and concludes that the targeting protein (NR-AN-01) binds to target cells within 5 minutes at low dose levels. Thus, Example 3 focuses specifically on the delivery of the targeted therapeutic conjugate.

Example 5 evaluates effects of a therapeutic conjugate which contains a targeting moiety on cellular activities in *in vitro* experiments. Example 5 provides no teaching about administration time *in vivo*.

Example 14 evaluates use of cytochalasin B as a "biological stent," a process involving inhibition of smooth muscle cell contraction, not inhibition of cell proliferation. Kunz provides no motivation for a person of ordinary skill in the art to use the administration method disclosed in Example 14, which is designed to achieve the biological stenting effect, for a method of inhibiting cell proliferation or treating hyperplasia. A person of ordinary skill in the art reading Kunz would not have had a reasonable expectation that inhibition of cell proliferation and treatment of

hyperplasia can be achieved by following the same administration method disclosed in Example 14 of Kunz.

Yapel does not cure the deficiency discussed above. Specifically, Yapel is cited as allegedly teaching use of albumin as a medicament carrier for intravascular injection. Yapel does not disclose method of treating non-cancerous cell proliferation in blood vessels, or systemically administering an effective amount of a nanoparticle drug composition in 30 minutes or less for such purpose.

Thus, Applicants respectfully submit that the cited references, alone or in combination, do not render claims of the present application obvious. Applicants respectfully request that the 35 U.S.C. § 103 rejection be withdrawn.

Rejection based on Hunter, Yapel, Kunz, Westesen, and Marx

Claims 36-37, 44-45, and 52-53 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hunter by itself or in view of Yapel in view of Kunz and Westesen in further in view of Marx (Circ. Res. Vol. 76, pp. 412-417, 1995, "Marx"). Applicants respectfully traverse.

As discussed above, Hunter, Yapel, Kunz and Westesen, alone or in combination, do not render claims of the present application obvious. Marx is cited as allegedly teaching rapamycin as an inhibitor of smooth muscle cells in the abnormal proliferation of restenosis. Marx does not cure the deficiencies discussed above.

Accordingly, Applicants respectfully submit that the cited references do not render claims of the present application obvious and request that the 35 U.S.C. § 103 rejection be withdrawn.

Double Patenting

Claims 1, 3-5, 7-14, 17, 31-33, 38-41, 46-49, 54-55, 57-96 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-2, 5-18 of copending application No. 11/594,417 in view of Hunter and Westesen. Claims 1, 3-14, 17, 31-33, 38-41, 46-49, 54-55, 57-96 are provisionally rejected on the ground of

nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-7, 11-20, 44-45 of copending application No. 11/359,286 in view of Hunter and Westesen.

Applicants respectfully request that these provisional projections be held in abeyance until the Office has made a determination of otherwise allowable claims in the present application or in copending Application Nos. 11/594,417 and 11/359,286.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 637782000127. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 12, 2009

Respectfully submitted,

Electronic Signature: /Jian Xiao/
Jian Xiao
Registration No.: 55,748
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-5736